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Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old

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AIMS

Little is known about the impact of inappropriate prescribing (IP) in community-dwelling adults, aged 80 years and older. The prevalence at baseline (November 2008September 2009) and impact of IP (misuse and underuse) after 18 months on mortality and hospitalization in a cohort of community-dwelling adults, aged 80 years and older (n = 503) was studied.

METHODS

Screening Tool of Older People's Prescriptions (STOPP-2, misuse) and Screening Tool to Alert to Right Treatment (START-2, underuse) criteria were cross-referenced and linked to the medication use (in Anatomical Therapeutic Chemical coding) and clinical problems. Survival analysis until death or first hospitalization was performed at 18 months after inclusion using Kaplan–Meier, with Cox regression to control for covariates.

RESULTS

Mean age was 84.4 (range 80–102) years. Mean number of medications prescribed was 5 (range 0–16). Polypharmacy (≥5 medications, 58%), underuse (67%) and misuse (56%) were high. Underuse and misuse coexisted in 40% and were absent in 17% of the population. A higher number of prescribed medications was correlated with more misused medications (r_s = .51, $P < 0.001$) and underused medications (r_s = .26, $P < 0.001$).

Mortality and hospitalization rate were 8.9%, and 31.0%, respectively. After adjustment for number of medications and misused medications, there was an increased risk of mortality (HR 1.39, 95% CI 1.10, 1.76) and hospitalization (HR 1.26, 95% CI 1.10, 1.45) for every additional underused medication. Associations with misuse were less clear.

CONCLUSION

IP (polypharmacy, underuse and misuse) was highly prevalent in adults, aged 80 years and older. Surprisingly, underuse and not misuse had strong associations with mortality and hospitalization.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Limited evidence on the clinical outcomes of screening tools for inappropriate prescribing exists.
- The effects of polypharmacy and misuse have mainly been studied in cross-sectional research, but little is known on the effects of underuse.
- Few studies of inappropriate prescribing specifically focused on the community-dwelling oldest old (aged 80 years and over).

WHAT THIS STUDY ADDS

- Polypharmacy, underuse and misuse were correlated and were coexistent in almost half of the oldest old population.
- Underuse was associated with increased rates of mortality and hospitalization, even when controlling for polypharmacy and misuse.
- For every additional underused medication at baseline, there was a 39% increased risk for mortality and a 26% increased risk for being hospitalized.The electronic application of explicit criteria can aid prescribers in detecting potential hazardous inappropriate prescribing, although further specification of these criteria is needed.

Introduction

Appropriate prescribing of medications is a major challenge in the care for older adults. Older adults are more sensitive to the effects of medications and have a higher prevalence of comorbidities [1]. Hence, older adults will have a higher medication intake, potentially putting them at risk for adverse drug events [2], increased morbidity, health care utilization and mortality [3]. Yet, polypharmacy cannot be equated with inappropriate prescribing (IP). IP is possible in polypharmacy, yet not every person with polypharmacy will have IP [4].

Prescribing can be potentially inappropriate if the potential benefits are outweighed by the harms, if there is evidence for an equal or more effective, yet lower risk alternative [5, 6] or if omission of potentially beneficial medications is present [7]. Tools were developed to identify inappropriate prescribing in older adults, focussing on polypharmacy, underuse and misuse [8]. Most of these tools consist of lists of explicit criteria of potentially inappropriate medications, often without the clinical data required. Some criteria address underuse instances, always requiring clinical data [9–11] and are designed to alert clinicians when to drop or add a medication in individual patients.

The clinical relevance of screening tools for inappropriate prescribing based on these explicit criteria is not yet fully explored. Most studies were cross-sectional. Gaps in evidence remain, as data from prospective long term cohort studies are scarce [12–15]. Moreover, the oldest old (aged 80 years and over) has been rarely studied as a separate group in primary care settings [16–18]. Finally, polypharmacy, underuse and misuse, although part of the definition of inappropriate prescribing, are seldom concomitantly studied [19].

This study aims to explore the prevalence of inappropriate prescribing (misuse and underuse) in a prospective cohort of community-dwelling oldest old (aged 80 years and over) and to explore associations with mortality and hospitalization after 18 months.

Methods

The Belfrail-Med cohort [20, 21] was used (n = 503), consisting of Belgian community-dwelling patients aged 80 years and over. All subjects were primary care patients, recruited by their own general practitioner (GP). Patients were selected between November 2008 and September 2009. Exclusion criteria were known dementia and in palliative care.

The GPs were responsible for the collection of baseline (demographic, clinical and medication data) and follow-up data (date and cause of death, date of the first hospitalization). Clinical research assistants were responsible to collect data from the patients, using clinical examinations (e.g. blood pressure, …), and standardized scales (to measure physical activity, activities of daily living…). GPs used their medical records.

Medication handling

The GP recorded all chronic medications at baseline, using the generic name. All chronic medications were codified entered into the Anatomical Therapeutic Chemical classification (WHO ATC/DDD 2013) [22], based on the official register of medications on the Belgian market.[1]

Polypharmacy was defined as the daily intake of five medications or more [23].

Assessing inappropriate prescribing

Inappropriate prescribing was operationalized by the computerized application of criteria for misuse and underuse. For misuse, we applied the clinically oriented Screening Tool for Older Person's Prescriptions (STOPP-2 criteria). For underuse, we applied the Screening Tool to Alert doctors to Right Treatment (START-2). These criteria are suitable for use in European countries [24], have been applied and validated in several studies [25–27] and were recently updated [10].

To assess the prevalence and impact of inappropriate prescribing, the STOPP/START–2 criteria were cross-referenced and linked to the baseline medications and clinical problems.

This was not possible for all criteria, as only a subset of the STOPP/START–2 criteria could be applied (see box 1). For the START-2 criteria, 13 out of 34 criteria could be used for our analysis and for the STOPP-2 criteria, 46 out of 81. Reasons to omit criteria included the absence of data in our database required by the criteria: (1) clinical test results, (2) severity of disease data, (3) short duration of medication and (4) criteria on rank ordering of first choice medications. Other

[1]Source: https://www.ehealth.fgov.be

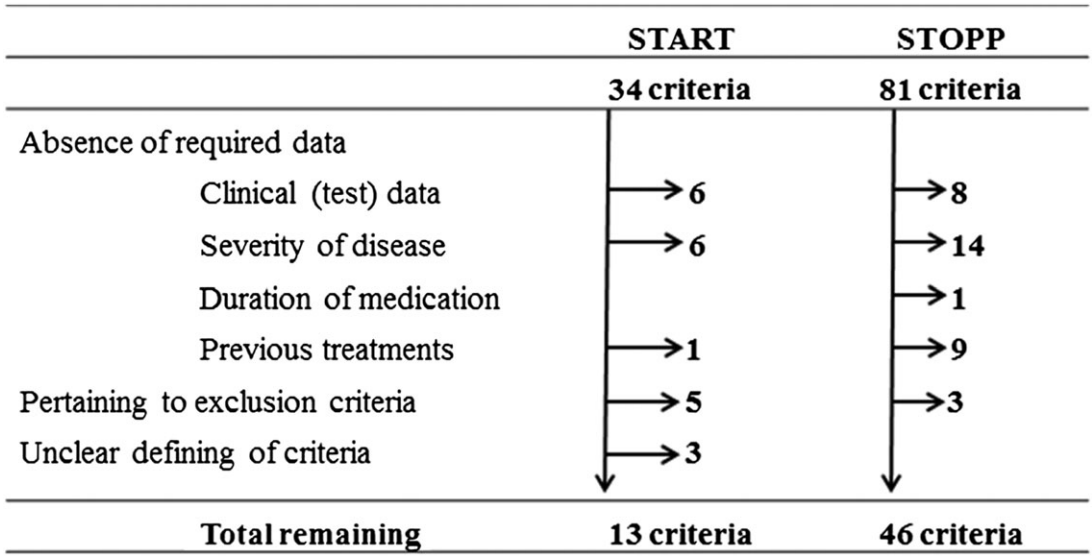
reasons to omit criteria were the unclear definition of clinical problems. Criteria pertaining to diseases excluded in our cohort (e.g. dementia) could also not be applied. Additionally for the STOPP-2 criteria, we omitted one extra criterion because of possible duplication in scoring. Criterion 32 (benzodiazepines for ≥4 weeks) and 74 (benzodiazepines could increase the risk of fall incidents) were considered too similar. For further analysis, only the former was taken into account. A full overview of the selection process can be found in box 1.

The Kaplan–Meier method was used to estimate the survival rate, with the log-rank test verifying the differences in survival time between groups. All deceased or hospitalized patients during the 18 months follow-up period were considered as 'events'. For hospitalization, additional censoring was done for patients who have died.

Cox proportional hazard models were used to calculate univariate and multivariate hazard ratios for associations with mortality and hospitalization. In univariate analysis,

Box 1

Flowchart for the rationale for exclusion of STOPP/START-2 criteria.



Outcome parameters

Follow-up data were collected using standardized questionnaires, filled in by the GPs. Data collection on mortality included date and cause of death. Data on hospitalization included the date of the first unplanned hospital stay (longer than 1 day). The full follow-up period of the Belfrail-study was 5 years [20], but to observe direct associations with baseline medication use, a shorter follow-up period was used, setting a cut-off at 18 months after inclusion in the cohort. All further analyses used the 18 months cut-off, although we provided in the text data on the 1 year survival rate for future and external comparisons.

Statistical analysis

SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) was used for analysis.

For all variables, there were less than 5% missing data [20]. Normally distributed continuous variables were expressed as means and .d.s. All skewed variables were expressed using the medians and interquartile ranges. Categorical data were expressed using numbers and percentages. Both underuse and misuse were divided into three categories, no (0), low (1–2) and high (3 or more) underuse or misuse of medications. Relationships between skewed data were tested using Spearman rank correlations.

we first tested the associations with inappropriate prescribing, expressed as a continuous variable. Second, we used the above described categories of underuse and misuse (no, low and high), to explore the associations with possible trends in higher mortality and hospitalization rates, for higher categories of underuse or misuse.

Lastly, we tested the interaction between underuse and misuse, by multiplying the number of underused and misused medications of each individual. The statistical significance of each interaction term was evaluated by the likelihood ratio test, comparing nested models with or without inclusion of the interaction term.

A similar exercise was repeated in the multivariate models for both the continuous and categorical variables for underuse and misuse. Now underuse and misuse (continuous and categorical) were corrected for the number of medications taken at baseline. Additionally underuse was corrected for misuse and misuse for underuse.

Ethical approval

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent

University Hospital (B670201421408, on 26/06/2014). All respondents provided informed consent.

Results

The patients in the Belfrail-Med cohort (n = 503) had a median age of 84.4 (range 80–102) years and 61.2% were female. Hypertension was the most common clinical problem, followed by osteoarthritis and hyperlipidaemia (see Table 1).

The mean number of medications was 5.4 (range 0–16). Cardiovascular (86.3%), haematological (56.1%) and nervous system drugs (54.5%) were most used.

Prevalence of inappropriate prescribing

Polypharmacy (≥ five medications) was present in 57.7% of the population. Using the START-2 criteria, underuse was identified in 67.0% of the population (range 0–5) and using the STOPP-2 criteria, misuse was identified in 56.1% (range 0–6).

In 17.1% of the population, no underuse or misuse was found. Only underuse was present in 26.8% and only misuse in 15.9%. The combination of underuse with misuse was present in 40.2% of the population (of which 31.4% had polypharmacy and 8.7% low medication use).

Table 1

Demographics and clinical characteristics of the study population (n = 503)

Demographic	Total (n = 503) %
Mean age in years (range)	84.4 (80–102)
Gender (% female)	61.2
Living alone	43.3
Nursing care at home	36.8
Low education (≤8 years)	69.2
Clinical[a]	**%**
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart failure (NYHA[a] **> 0)**	38.4
Obesity (BMI > 30 kg m^{-2})	27.9
Osteoporosis	20.9
Diabetes	18.9
Post-myocardial infarction/post-stroke	17.7
COPD/asthma	13.1
Depression	12.7
Chronic renal failure	11.1

[a]Clinical problems with prevalence above 10% are listed
[b]New York Heart Association (NYHA) functional classification of heart failure

The most prevalent criterion for underuse was the absence of an angiotensin converter enzyme inhibitor in patients with systolic heart failure (26%) and the absence of antiplatelet therapy in patients with documented coronary, cerebral or peripheral vascular disease (24%). The most prevalent criterion for misuse (35%) was the intake of benzodiazepines for longer than 4 weeks (see box 2 for the prevalence of other criteria).

Box 2

Flowchart for the rationale for exclusion of STOPP/START-2 criteria.

Inappropriate prescribing	Most identified	%
Underuse	Angiotensin converting enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	26.2
	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	24.3
	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years	14.9
	Regular inhaled β_2-adrenoceptor agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD	10.5
	Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (bone mineral density T-scores more than −2.5 in multiple sites)*	9.1
Misuse	Benzodiazepines for ≥4 weeks	35.2
	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	12.5
	Antimuscarinic drugs with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism**	10.7
	Use of regular (as distinct from p.r.n.) opioids without concomitant laxative (risk of severe constipation)	7.8
	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	3.4

*Only the clinical indicator osteoporosis could be used. Fragility fractures and bone mineral density scores were not available. **The clinical indicator dementia was an exclusion criteria for this cohort

Association of inappropriate prescribing with the amount of medications taken

The Spearman rank correlation between the number of medications taken, underuse and misuse is shown in Table 2. The number of medications showed a high positive correlation with misuse (r_s 0.51, $P < .001$), and with underuse (r_s 0.26, $P < .001$). Moreover, there was also a statistically significant

Table 2

Description of the medication use and level of inappropriate prescribing

Description of the medication use		Mean (range)
Medication use		5.4 (0–16)
Underuse		1.2 (0–5)
Misuse		0.9 (0–6)
		%
Polypharmacy (≥five drugs daily)		57.7
ATC C - Cardiovascular		86.3
ATC B - Blood and blood forming		56.1
ATC N - Nervous system		54.5
ATC A - Alimentary tract and metabolism		50.1
ATC M - Musculo-skeletal system		23.5
ATC R - Respiratory system		15.9
ATC H - Systemic hormonal preparations		11.7
ATC G - Genito-urinary system and sex hormones		10.3
Inappropriate prescribing	**Underuse %**	**Misuse %**
0	33.0	43.9
1–2	52.7	46.7
3 or more	14.3	9.3
Combinations	**Low medication use (0–4), in %**	**Polypharmacy (5 or more), in %**
No misuse or underuse	12.5	4.6
Only underuse	15.3	11.5
Only misuse	5.8	10.1
Underuse and misuse	8.7	31.4
Correlations[a]		**r_s (*P* value)**
Underuse * Misuse		.19 (<0.001)
Underuse * Number of medications		.26 (<0.001)
Misuse * Number of medications		.51 (<0.001)

[a]All variables are expressed as continuous variables

correlation between underuse and misuse, in the positive direction (r_s 0.19, $P < .001$).

Survival analysis of inappropriate prescribing on mortality and hospitalization

The mortality rate after18 months was 8.9% ($n = 45$) and the hospitalization rate 31% ($n = 156$). Causes of death included cardiovascular and/or cerebrovascular related events (48.9% of deaths), cancer (20.0%),respiratory related events (13.3%) or general deterioration (6.7%).

The survival analysis showed a significant difference between different categories of underuse for both mortality and hospitalization (log rank $P < 0.001$). The survival rates for mortality after 18 months for those with no, low (1–2) and high underuse (3 or more) were, respectively, 97%, 96% and 88% (see Figure 1). The survival rates for hospitalization after 1 year were, respectively, 85%, 81% and 59% (see Figure 2).

For misuse, no significant difference was found for both outcomes.

Univariate analysis for the impact of inappropriate prescribing

In our previous analysis of polypharmacy, we observed a significant association of the number of medications with mortality and with hospitalization [28]. Here, we also looked concomitantly at the additional effects of underuse and misuse (see Table 3). For mortality, underuse expressed as a continuous variable, showed an increased risk (HR 1.43, 95% CI 1.15, 1.78). In categorical analysis, patients with high underuse (three or more) had a 3.3 fold significantly increased risk for mortality compared with those with no underuse. Misuse did not show a significant association with mortality (see Table 3).

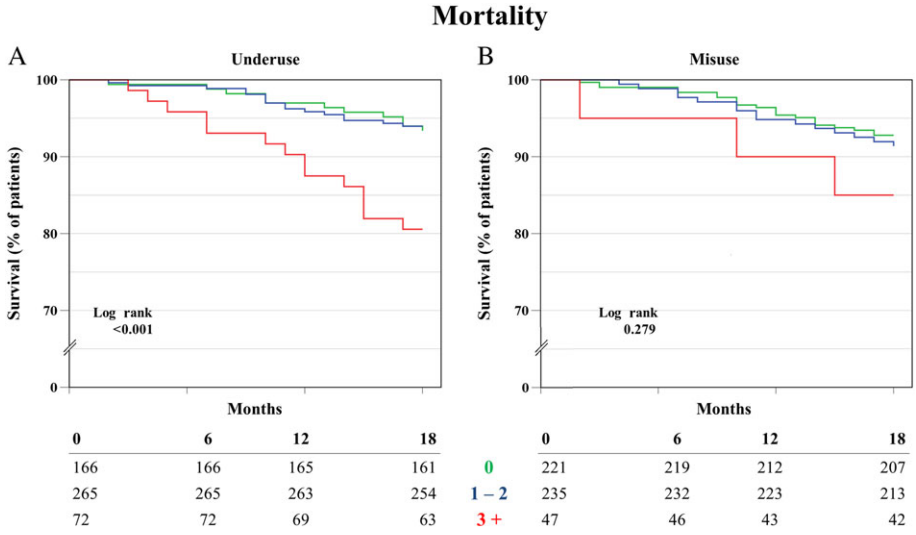


Figure 1

Kaplan-Meier Survival analysis of time to death for groups of underuse (A), and groups of misuse (B)

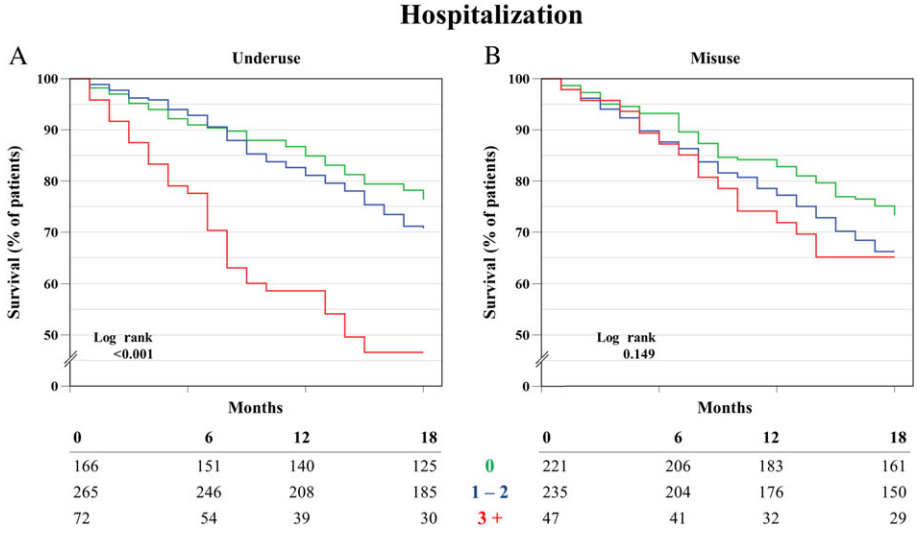


Figure 2

Kaplan-Meier survival analysis of time to first hospitalization for groups of underuse (A), and groups of misuse (B)

For hospitalization, underuse expressed as a continuous variable showed an increased risk as well (HR 1.35, 95% CI 1.19, 1.54). In categorical analysis, patients with high underuse (3 or more) had a 2.8 fold significantly increased risk for being hospitalized, compared with those with no underuse. Misuse, yet only when expressed by the continuous variable, showed an increased risk for hospitalization (HR 1.20, 95% CI 1.06, 1.36), but not for mortality.

The interaction effect (multiplying underuse with misuse, range 0–24) was significant as well, for both mortality (HR 1.07, 95% CI 1.00, 1.15, $P = 0.044$) and hospitalization (HR 1.08, 95% CI 1.04, 1.12).

Multivariate analysis for the impact of inappropriate prescribing

The results of the multivariate analysis are shown in Table 4. After correction for the number of medications and for the number of misused medications, underuse. expressed continuously and categorically, showed significant increased risks for mortality and hospitalization. For every additional underused medication at baseline we observed a 39% increased risk for mortality and a 26% increased risk for hospitalization after 18 months. Compared with those with no underuse, those with high underuse (three or more) showed a 2.9 fold increased risk for mortality and a 2.1 fold risk for hospitalization.

Table 3

Univariate Cox regression analysis of mortality (8.9%) and hospitalization (31.0%) in association with inappropriate prescribing in a cohort of oldest old (n = 503)

Continuous		Range	Mortality HR (95% CI)	Hospitalization HR (95% CI)
Number of mediations		0–21	1.12 (1.02, 1.22)	1.14 (1.08, 1.20)
Underuse		0–5	1.43 (1.15, 1.78)	1.35 (1.19, 1.54)
Misuse		0–6	1.16 (0.92, 1.47)	1.20 (1.06, 1.36)
Interaction effects				
Underuse*Misuse		0–24	1.07 (1.00, 1.15)	1.08 (1.04, 1.12)
Categorical	**Cut-offs**	***n***	**Mortality HR (95% CI)**	**Hospitalization HR (95% CI)**
Underuse	0	166	1	1
	1–2	265	.89 (.43, 1.86)	1.17 (.81, 1.71)
	3 or more	72	3.33 (1.58, 7.04)	2.79 (1.79, 4.34)
Misuse	0	221	1	1
	1–2	235	1.52 (0.80, 2.90)	1.33 (0.95, 1.86)
	3 or more	47	1.95 (0.7, 5.03)	1.49 (0.87, 2.55)

The associations of inappropriate prescribing were first tested, using the continuous variables for underuse and misuse. Using categorical analysis, trends were explored for a higher risk for mortality or hospitalization with a higher degree of underuse or misuse

Table 4

Multivariate Cox regression analysis of mortality (8.9%) and hospitalization (31.0%) in association with inappropriate prescribing in a cohort of oldest old (n = 503)

Continuous	Range		Mortality HR (95% CI)	Hospitalization HR (95% CI)
Underuse	0–5		1.39 (1.10, 1.76)[a]	1.26 (1.10, 1.45)[a]
Misuse	0–5		0.93 (0.69, 1.24)[b]	.98 (.84, 1.14)[b]
Categorical	**Range**	***n***	**Mortality HR (95% CI)**	**Hospitalization HR (95% CI)**
Underuse	0	166	1	1
	1–2	265	.88 (0.41, 1.90)	1.04 (.71, 1.53)
	3+	72	2.91 (1.28, 6.61)[a]	2.08 (1.29, 3.36)[a]
Misuse	0	221	1	1
	1–2	235	1.16 (0.58, 2.34)	.96 (.67, 1.38)
	3+	47	1.07 (0.36, 3.17)[b]	.74 (.41, 1.36)[b]

The associations of inappropriate prescribing was first tested using the continuous variables for underuse and misuse. Using categorical analysis, trends were explored for a higher risk for mortality or hospitalization with a higher degree of underuse or misuse

[a]Underuse was corrected for the number of medications and for the number of misused medications

[b]Misuse was corrected for the number of medications and for the number of underused medications

Misuse, after controlling for the number of medications and underuse, did not show significant associations with both mortality and hospitalization.

Discussion

To the best of our knowledge, this study is the first prospective longitudinal cohort study of community-dwelling older adults, aged 80 years and more, exploring the associations of inappropriate prescribing with mortality and hospitalization, using a computerized version of the STOPP/START–2 criteria.

Main findings

First, we observed a high prevalence of polypharmacy (58%), concurrent with a high prevalence of underuse (67%) and misuse (56%). The combination of polypharmacy, underuse

and misuse was present in 31% of the population. Only in 9% of the population, no polypharmacy, no underuse and no misuse were observed.

Second, the Spearman rank correlations suggest that the number of medications were positively correlated with the number of misused medications and also with the number of underused medications.

Lastly, our main finding is that every additional underused medication was associated with a relative increase in mortality rate of 39% and in a hospitalization rate of 26% after 18 months, independent of the number of medications taken and of the number of misused medications.

Limitations of this study

Results of this observational study do not allow causal relations. The relation between inappropriate prescribing and mortality and hospitalization was established out of the proof of a (chronic) inappropriate medication intake throughout the study period. Also, the results cannot be generalized beyond the population of cognitive fit community-dwelling older persons.

The negative results need to be interpreted with caution, especially the absence of associations with misuse, as the sample size may have resulted in underpowered statistical analysis for this aspect. Additionally, we did not use the full STOPP/START–2 criteria, only those that were applicable in our database and suitable for the computerized evaluation. Also, other authors have made partial use of the STOPP/START criteria for pragmatic reasons [29]. However, the criteria applied in this study matched with the most prevalent criteria in other studies [10, 19, 30–33]. Nevertheless, the true prevalence of inappropriate prescribing could have been underestimated in this study. To check this issue for misuse, we repeated the same analysis with the medication only EU(7)-PIM list [34], also focussing on misuse. Again, only in univariate analysis, we observed a limited association of misuse with hospitalization and not with mortality. All associations of misuse disappeared after entering the number of medications and underuse into the multivariate model.

In our database of prescriptions, over the counter drugs were not included, also possibly underestimating the prevalence of misuse.

Comparison with other findings

In our study, there was a high prevalence of polypharmacy (58%), underuse (67%) and misuse (56%). Interpretation and comparison of the prevalence of inappropriate prescribing must be done with caution, since most studies either used younger aged populations or used the STOPP/START–1 criteria. In other studies, underuse ranged between 23–58% [10, 18, 35–37] and misuse ranged 21–60% [17, 18, 36–38]. For underuse, our results were over the upper limit of this range and the results for misuse were close to the upper limit of the range.

Cross-sectional studies focussing on younger age groups and using the Beers [39–41] or STOPP/START–1 [33] criteria have shown higher prevalence of inappropriate prescribing in those who were hospitalized. Associations with mortality have been observed as well, although only in older hip fracture patients [42].

Comparison with the scarce existing longitudinal cohort studies is difficult, as these studies focussed on younger adults (65 years and over), on those in nursing homes, or studied other outcomes such as adverse drug events, economic costs, or geriatric syndromes (falls) [12–14].

The impact of underuse has also been observed in another cohort, focussing on cardiovascular patients (aged 50–74 years) [15, 43, 44].

Implications for research

This study clearly indicated that higher underuse was associated with higher mortality and with higher hospitalization rate. As this observational study allows no causal inference, we can only formulate hypotheses for further research.

The results of this study suggest that the underuse of medications, next to polypharmacy, was strongly associated with outcomes. An explanation could be the reluctance of GPs to prescribe additional medications in patients with a high multimorbidity and polypharmacy [45, 46] or of a possible aversion of patients for new therapies. The lack of clear evidence of some pharmacotherapies in the oldest age groups may explain reluctance of GPs to adhere to general treatment recommendations in this age group [47]. However, most of the START criteria are evidence-based and should not be overridden.

In addition, deprescribing or not starting medications might be caused by a perception of futility in the face of approaching death in this population. In case this clinical perception is true, this could lead to a higher morbidity in the group of those with underuse, making mortality more the cause rather than the consequence of underuse. However, it should be remembered that this cohort was limited to community-dwelling active and cognitively fit oldest old, not in palliative care. Another hypothesis could be that substandard prescribing in older adults is a physician trait [48] and an instrumental variable that leads to a combination of polypharmacy, underuse, misuse and higher mortality/hospitalization.

Applicability of the STOPP/START criteria in a particular patient has until now most often been based on the human judgement of a clinical pharmacologist (or similar). Our study indicates that the electronic application of the STOPP/START–2 criteria is feasible, but that further specification of clinical problems and medication groups in the light of computerization is needed [49]. Large scale application on big data will need substantial progress in semantic interoperability of clinical data in heterogeneous electronic health records [49–51].

Implications for practice

The interpretation and transferability of the results to other care settings or other patients must be done with caution. The Belfrail-med cohort excluded those in nursing homes, those with known dementia and those in palliative care. These community-dwelling oldest old patients can be considered as the most active and healthy in this age segment.

The findings of our study are in favour of using the STOPP/START–2 criteria in clinical practice or for education purposes of clinicians. They are adapted to European medication markets and can detect underuse.

Using a cut-off for polypharmacy, with a simple arbitrary point (e.g. ≥ five medications) or as a sole indicator for quality is problematic. Polypharmacy can be a risk for worse outcomes, even when all prescribed medications are justified. In this study, underuse of medications that should have been prescribed for a specific indication may also be hazardous. Our present and previous results indicate that a more patient-tailored approach is needed to solve this dilemma [28]. The discussion on too much medication or too unsafe needs more differentiation and a clear assessment of misuse and underuse using full knowledge on the patient, his/her comorbidities and his/her medications. Computerization of the analysis of medication lists should be considered as a facilitator of the data collection process and the medication chart review, but not as a substitute for assessment of the pharmacological therapy of an individual patient.

In conclusion, inappropriate prescribing (polypharmacy, underuse and misuse) was highly prevalent in community-dwelling adults, aged 80 years and older. Underuse and misuse were highly correlated and coexisted in almost half of the population. Surprisingly, underuse and not misuse had strong associations with mortality and hospitalization, even when controlling for polypharmacy and misuse. Incentives towards patient-tailored appropriate prescribing in older adults are needed, taking the number of medications, underuse and misuse into account.

Competing Interests

All authors declare no conflict of interest. All authors have completed the ICMJE uniform disclosure form. There was no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

All authors contributed to this work. B.V., J.D. and O.D. were responsible for conducting the Belfrail study, including data collection. M.A. entered the medication data. M.W. was responsible for analyzing and writing this paper. T.C., R.V.S., M.E. and M.A. contributed in the statistical analysis, interpreting and discussing the results and writing of the paper as well. All authors were responsible for revising this work critically for important intellectual content. All authors are accountable for all aspects of the work.

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Addendum S1 STOPP/START–2 criteria that were and were not applied (inclusive rationale for omitting criteria)